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The Fibrosis Across Organs Symposium: A Roadmap for Future Research Priorities

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AUTHORS' CONTRIBUTIONS

We applied a combined SDC, EC, FLAE and PCI approach for the sequence of authors. First Authorship will be shared by: JR, TRB and DJK.

Symposium conceptualization: TRB, JDT, GPC, DJK, DED, KKB and SC.

Symposium leadership, speaker and workgroup leader selection and content management: GPC, TRB, DJK, KKB, DED, SC and JDT.

Manuscript preparation and ?nal approval: JR, TRB, DJK, GPC, DED, AMT, LR, ESW, DAB, LMS, TDH, BIJ, TAM, JDT, SC and KKB.

TRB was formerly with National Jewish Health.

CONFLICT OF INTEREST

The symposium was convened by the American Thoracic Society and supported by sponsorships from the following organizations; Boehringer Ingelheim Pharmaceuticals, Inc., Celgene Corporation, the Coalition for Pulmonary Fibrosis, Genentech, Gilead Sciences, Inc., Hermansky-Pudlak Syndrome Network, Inc., InterMune, Inc., the Pulmonary Fibrosis Foundation, Sanofi US and Stromedix. Symposium sponsors had no input in the development of the symposium content, selection of speakers or in the development of this manuscript.

GPC has served as site PI or collaborator in industry-sponsored clinical trials (Genzyme and Bristol Myers Squibb). He serves as the Chief Medical Officer of the Pulmonary Fibrosis Foundation and has served as an advisor to InterMune and Boehringer Ingelheim. DJK reports personal fees from Boehringer-Ingelheim, outside the submitted work; and was formerly Vice President of Patient Relations and Medical Affairs at the Pulmonary Fibrosis Foundation. TRB reports nonfinancial support from American Thoracic Society, personal fees from Coalition for Pulmonary Fibrosis, grants from InterMune, outside the submitted work. JR has served as site PI or collaborator in industry-sponsored clinical trials (Gilead, InterMune, ImmuneWorks, Boehringer Ingelheim, Bristol Myers Squibb) and is funded by the National Institutes of Health and the Department of Veterans Affairs. He serves on the Boards of the Pulmonary Fibrosis Foundation and the American Lung Association-Midland States. ESW reports grants from NIH, during the conduct of the study; personal fees from Boehringer-Ingelheim, personal fees from Kadmon Corporation, outside the submitted work. He serves on the Medical Advisory Board of the Pulmonary Fibrosis Foundation. AMT has received grant support from the National Institutes of Health, Biogen, Boehringer Ingelheim and InterMune, and has served on the Scientific Advisory Board of Amira Pharmaceuticals and PharmAkea Therapeutics, and the Medical Advisory Board of the Pulmonary Fibrosis Foundation. LR reports grants and personal fees from Boehringer Ingelheim, during the conduct of the study; grants and personal fees from InterMune, personal fees from Medimmune, personal fees from Biogen-Idec, personal fees from Sanofi-Aventis, personal fees from Roche, personal fees from Takeda, personal fees from ImmuneWorks, personal fees from Shionogi, outside the submitted work. T.D.H. reports grants from The National Health and Medical Research Council of Australia (NHMRC), nonfinancial support from Novartis, outside the submitted work. TAM has nothing to disclose. KKB reports no relevant potential conflicts. DED reports personal fees: honoraria from Boehringer Ingelheim for lectures on pulmonary fibrosis outside of submitted work. DAB has nothing to disclose. SC was formerly the Executive Director of the American Thoracic Society (ATS) and has no other disclosures to report. The ATS received grants from Boehringer Ingelheim Pharmaceuticals, Inc., Celgene Corporation, the Coalition for Pulmonary Fibrosis, Genentech, Gilead Sciences, Inc., Hermansky-Pudlak Syndrome Network, Inc., InterMune, Inc., the Pulmonary Fibrosis Foundation, Sanofi US, and Stromedix, in support of the conduct of the symposium. SC reports grants from Boehringer Ingelheim, grants from Genentech, grants from InterMune, grants from Gilead, grants from Sanofi, grants from Celgene, grants from Hermansky Pudlak Foundation, grants from Coalition for Pulmonary Fibrosis, grants from Stromedix, grants from Pulmonary Fibrosis Foundation, during the conduct of the study. BIJ has nothing to disclose. JDT has nothing to disclose.

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HISTORICAL CONTEXT

The ability to develop discrete areas of tissue fibrosis or scarring represents a normal physiologic response to injury that is necessary for the maintenance of tissue integrity and normal organ function. In contrast, uncontrolled, dysregulated fibroproliferation and abnormal matrix deposition/remodeling results in tissue fibrosis and organ dysfunction, regardless of the initiating event.[1] The latter process underlies a wide variety of clinically significant disorders ranging from idiopathic pulmonary fibrosis (IPF) and liver cirrhosis to kidney sclerosis and cutaneous fibrosis. However, the mechanisms responsible for injury responses that lead to tissue fibrosis in these organs are incompletely understood. With an enhanced understanding of the mechanisms responsible for both physiologic and dysregulated fibrosis across several organ systems, common fibrotic pathways may be identified and potential targets for intervention can be unveiled. Unfortunately, research in fibrogenesis in distinct organs has been conducted largely independently, with very few examples of collaborative investigations into the common and/or divergent pathways of tissue fibrosis in different organs. In the lung, for example, excessive fibroproliferation and tissue remodeling can occur in response to several defined environmental and occupational exposures or systemic illnesses. However, in idiopathic pulmonary fibrosis, the eliciting cause is unknown and the mechanisms responsible for its progression are unclear, but both genetic and environmental factors have been implicated. Similar fibrosing phenomena

appear in other organs, but whether there are shared or divergent mechanisms of action among them remains uncertain.[2–4]

To promote collaboration and the exchange of information amongst investigative teams focused on distinct organs, the American Thoracic Society convened the *Fibrosis Across Organ Symposium* with the intention of defining gaps in knowledge and priority areas for investigation. The meeting was held in Denver, Colorado, USA, in 2012, but the meeting proceedings were never published. Considering the perceived importance of the deliberations held, participants came together to summarize the discussions in this document.

The organizers invited participants based on their expertise in the investigation of fibrogenesis as evidenced by their international reputation, publications and presentations at international conferences. Participants with expertise in fibrosis in lung, liver and heart, among other organs, were asked to review topics relevant to their area of expertise focusing on shared versus organ-specific mechanisms of fibrogenesis from which key insights may be gleaned. Prior to the conference, participants were asked to identify and submit "5 Questions" which they would like to answer over the next several years of investigation, and to rank them in order of priority. These questions served as a template for discussion in both the plenary sessions and in the breakout, workshop sessions. This technique is a modification of the Delbecq nominal-group interactive method, and ensures that all participants' positions are aired in an anonymous and/or open-forum fashion.[5] This technique further ensures that all participants' thoughts are equally considered in the breakout groups and in the final session where consensus recommendations are finalized by all participants. The following key concepts of fibrogenesis were explored: (1) mechanisms of injury leading to fibrosis, (2) mechanisms of fibroproliferation, (3) mechanisms of wound healing and (4) mechanisms of antifibrogenic therapies. Participants with varied clinical and basic science backgrounds were assigned to 1 of the 4 working groups focused on these concepts. Each group was responsible for reviewing our current knowledge, including *in vitro* and *in vivo* model systems; identifying the important knowledge gaps; and determining the critical "next questions" that need to be answered to allow progress, while defining short- and long-term research priorities. Following the initial plenary sessions, participants broke into 1 of 4 working groups based on the key concepts and generated key priority questions considered critical for exploration to advance the field.

PRIORITIES AND GAPS IN KNOWLEDGE IDENTIFIED

Working Group I-Mechanisms of Injury Leading to Tissue Fibrosis

Although the specific tissue injury in some fibrosing disorders is known, many fibroproliferative disorders are idiopathic. This complicates the exploration of the mechanisms leading to tissue fibrosis. However, there is a general sense that, while a variety of tissue injuries might trigger a set of cellular signals common to multiple tissues and disorders, other signals may be tissue or organ-specific, and that studying these divergent pathways might provide important insight.[1] By the date of the symposium, there had been limited systematic efforts designed to identify signaling pathways or patterns of gene

expression unique to fibrosis in specific organs, yet publicly available data sets are available and can be interrogated for this purpose.

Priorities and Key Gaps of Knowledge

- What initiates the tissue injury in clinically significant diseases characterized by tissue fibrosis?
- What profibrogenic pathways are common among different organs?
- What profibrogenic pathways are divergent among different injured organs?

Working Group II-Mechanisms of Fibroproliferation

The fundamental mechanisms of fibroproliferation have been intensely investigated over the past several decades. These efforts have implicated genetic predisposition, cellular inflammation, tissue remodeling, oxidative and endoplasmic reticulum stress, autophagy and aging, among other mechanisms in the initiation and propagation of fibrosis.[2,6] Models best suited to investigate fibroproliferation are evolving, but remain narrowly defined and context specific.

Priorities and Key Gaps of Knowledge

- What is the role of inflammation in tissue fibrosis and does it differ amongst organs?
- How does aging predispose individuals to fibrosis?
- Which cellular components drive fibroproliferation during the early and late stages after injury, and from where do they originate?

Working Group III-Mechanisms of Wound Healing

The response to injury, and more importantly its resolution with minimal dysfunction, is an essential homeostatic response regardless of the type and site of injury.[7,8] Significant emphasis has been placed on the initiating events leading to cellular and tissue injury due to the available animal models.[9] These models generally fail to simulate human disease, which is often characterized by chronic and progressive fibrosis. Additional approaches which also emphasize the resolution phase of injury might help accelerate our understanding of this inherently complex process.

Priorities and Key Gaps of Knowledge

- What promotes adaptive vs. maladaptive wound healing during the reparative process triggered after injury?
- What can be learned from comparing models of permanent versus reversible fibrosis?
- Are there models of tissue fibrosis that capture the chronic and progressive fibroproliferative disorders seen in humans?

- Is fibrosis permanent or can it be reversed, as seen in fetal injuries and some disorders in adults?

Working Group IV-Mechanisms of Antifibrogenic Therapies

The identification of efficacious therapies for chronic fibrosing diseases has been challenging because of our rudimentary understanding of the pathobiology of the diseases in question.[4] However, data generated in animal models and through clinical studies, and studies using new genomic technologies, have unveiled observations that will inform future investigations particularly in prognostication and novel therapies.[10,11] These approaches applied across different organ systems might help identify common risk factors and mechanisms as well as potential targets for intervention. (Note that antifibrotic drugs approved for the management of IPF emerged after this symposium was held.)

Priorities and Key Gaps of Knowledge

- What is the potential role of stem cells (e.g., iPS, hematopoietic) and regulatory T cells in the development and/or treatment of fibrosis?
- Are there polymorphisms / epigenetic modifications that predispose individuals to fibrosis?
- How can the response to therapy be better assessed clinically?
- Are there common biomarkers capable of defining degree or stage of fibrosis?
- Are there imaging techniques able to quantify the degree of fibrosis and response to therapy?

PRIORITIES FOR FUTURE INVESTIGATION

Following the breakout sessions and identification of priority questions, the entire group developed the following recommendations and identified opportunities for future research directions.

- Develop a universal definition of fibrosis that may be applied to different tissues, including standard ways to measure and grade degree of fibrosis.
- Develop a systematic program to delineate the mechanisms associated with aging that predispose individuals to fibrosis and organ dysfunction.
- Continue investigations into embryonic wound healing and the distinct differences that limit fibrogenesis in these tissues in contrast to those in adults.
- Determine how genetic and environmental factors interact to predispose individuals to the development of fibrosis.
- Develop and validate novel models that more robustly simulate human fibrotic disease.
- Develop improved modalities to quantify fibroproliferation so that more durable and practical endpoints of therapy can be utilized.

- Continue the identification and validation of indirect and direct biomarkers of fibrotic diseases.
- Promote the development of a cellular and tissue repository of fibrotic tissue samples from multiple organs to allow for rapid screening for potentially "common" fibrogenesis pathways.
- Develop an integrated approach for subcellular to tissue level investigations, combined with translational and clinical research to comprehensively investigate the complex and shared processes that directly or indirectly lead to significant disability and death related to fibrosing disorders.
- Perform comparative analyses of molecular, genetic and epigenetic data generated in organ specific human fibrosis.
- Establish an interdisciplinary "Fibrosis Network" of investigators to identify common interests and expedite investigations.
- Identify shared resources such as *in vitro* and *in vivo* models of fibrosis as well as reagents to facilitate investigations.
- Convene a workshop to further interrogate potential mechanisms of fibrosis utilizing a comparative analysis approach.
- Expand future Fibrosis Across Organs Symposia to a more diverse field of investigators with enhanced representation from experts in quantitative imaging, pathology and systems biology.

CONCLUSIONS

The goal of the 2012 Fibrosis Across Organs Symposium was to identify important gaps in our knowledge of fibroproliferation, identify mechanisms shared across or divergent among different organ systems, and establish a framework for research in the field. At the time the symposium was held, organizers believed the concept would take hold in the scientific community and become an area of focus in the years that followed. Since the symposium, the Fibrosis Across Organs concept has had some success in moving fibrosis research forward as several centers across the country now hold regular meetings with their scientific experts in fibrosis across organs, collaborations have formed to carry out novel research projects in multiple areas of fibrotic disease, and new fibrosis research centers are being created. More recently, the National Heart, Lung and Blood Institute of the National Institutes of Health published its recommendations for the next decade of work in lung fibrosis and in its report identified fibrosis across organs as a priority area. In 2015, the NIH established a new mechanism for research funding for Fibrosis Across Organs representing $10.8 million in funding for multiorgan fibrosis projects until year 2020 (http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-16-003.html). Although signs of progress driven by this effort have emerged since the symposium, much more needs to be done to take advantage of the knowledge generated through organ-specific tissue fibrosis research and accelerate discovery through collaborative initiatives. It is the expectation of the organizing team that through an integrated approach and collaborative efforts, the priorities

for future investigation identified above will be systematically addressed to advance our understanding of and care for patients with devastating organ fibrosis.

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Working Group I-Mechanisms of injury leading to fibrosis. *Speakers*: Zea Borok, MD; Sonye Danoff, MD, PhD; Andreas Guenther, MD; Timothy McKinsey, PhD. *Breakout Session Leaders*: Eric S. White, MD; Jerry Eu, MD; Peter Henson, PhD, MD; Moises Selman, MD.

Working Group II-Mechanisms of fibroproliferation. *Speakers*: Erica Herzog, MD PhD; Claude Jourdan LeSauux, PhD; David A. Brenner, MD; Harold Chapman, MD. *Breakout Session Leaders*: Neil Henderson PhD; Daniel Kass, MD; Timothy Blackwell, MD PhD; William Travis, MD.

Working Group III-Mechanisms of wound healing. *Speakers*: Shawn Cowper, MD; Eric S. White, MD; Lynn Schnapp, MD; Timothy Hewitson, PhD. *Breakout Session Leaders*: Luca Richeldi, MD PhD; Jack Elias, MD; Dennis E. Doherty, MD; Martin Kolb, MD, PhD.

Working Group IV-Mechanisms of antifibrotic therapies. *Speakers*: David A. Schwartz, MD; Andrew M. Tager, MD; Neil Henderson, MD, PhD; Bodh I. Jugdutt, MBchB, MSc, MD, FRCP. *Breakout Session Leaders*: Tatiana Kisseleva, PhD; Andrew M. Tager, MD; Jesse Roman, MD; Ganesh Raghu, MD.

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